COOPERATIVE STUDY GROUP FOR AUTOIMMUNE DISEASE PREVENTION

Release Date: September 7, 2000

RFA: AI-00-016

National Institute of Allergy and Infectious Diseases
(http://www.niaid.nih.gov/)
National Institute of Diabetes and Digestive and Kidney Diseases
(http://www.niddk.nih.gov/)
National Institute of Child Health and Human Development
(http://www.nichd.nih.gov/)
National Institute of Dental and Craniofacial Research
(http://www.nidcr.nih.gov/)
National Institute of Arthritis and Musculoskeletal and Skin Diseases
(http://www.nih.gov/niams)
Office of Research on Women's Health, National Institutes of Health
(http://www4.od.nih.gov/orwh/)
The Juvenile Diabetes Foundation International
(http://www.jdf.org/)

Letter of Intent Receipt Date: December 15, 2000
Application Receipt Date: February 26, 2001

APPLICATIONS IN RESPONSE TO THIS REQUEST FOR APPLICATIONS (RFA) MUST BE PREPARED USING SPECIFIC INSTRUCTIONS IN AN NIAID BROCHURE ENTITLED "INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS" available at: http://www.niaid.nih.gov/ncn/tools/multibron.htm.

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Dental and Craniofacial Research (NIDCR), the Office of Research on Women's Health (ORWH), National Institutes of Health (NIH), and the Juvenile Diabetes Foundation International (JDFI) invite applications from single institutions or consortia of

institutions to participate in the Cooperative Study Group for Autoimmune Disease Prevention. The purpose of this program is to support a closely interactive and collaborative network of investigators in a unique study group to focus on autoimmune disease prevention. This group will: 1) advance the understanding of immune homeostasis in autoimmune diseased states as well as non-diseased states, including the pediatric immune response, and 2) build the knowledge base needed to develop interventions for the prevention of human autoimmune diseases, with special emphasis on type 1 diabetes. The Cooperative Study Group will engage in collaborative and individual projects focused on understanding the immune mechanisms that underlie autoimmunity and autoimmune diseases, mechanisms and consequences of manipulation of the immune response in autoimmunity, and application of this information to the prevention of autoimmune disease in humans. For the purpose of this RFA, “prevention of autoimmune disease” is defined as halting the development of an autoimmune disease prior to clinical onset by mechanisms other than global immunosuppression.

Each application must include a minimum of three projects; at least one project must focus directly on type 1 diabetes; applications that include projects on other autoimmune diseases or projects related to more than one disease are particularly encouraged, however, applications may focus entirely on diabetes. Animal studies are allowed under this RFA, but the applicant must document the relevance of such models to development of preventive strategies for humans. Applications from consortia of institutions are strongly encouraged to ensure that the scope of scientific expertise necessary to meet the requirements of this RFA is available. All applicants must comply with the requirements outlined in the section below entitled "SPECIAL REQUIREMENTS."

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS led national activity for setting priority areas. This Request for Applications (RFA), “COOPERATIVE STUDY GROUP FOR AUTOIMMUNE DISEASE PREVENTION,” is related to the focus area of diabetes and chronic disabling diseases. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

ELIGIBILITY REQUIREMENTS

Research grant applications may be submitted by domestic for-profit and non-profit organizations, public and private institutions, such as universities, colleges, hospitals, laboratories, units of State

and local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible to apply, but applications from United States institutions may include foreign components. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

The administrative and funding mechanism to be used to undertake this program will be the Multiproject Cooperative Agreement (U19), an "assistance" mechanism, rather than an "acquisition" mechanism. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but NIH is not to assume direction, prime responsibility, or a dominant role in the activity. Essential elements of the multiproject cooperative agreement mechanism also include: (1) a minimum of three interrelated individual research projects organized around a central theme; (2) collaborative efforts and interaction among independent projects and their investigators to achieve a common goal; (3) a single Principal Investigator who will be scientifically and administratively responsible for the group effort; (4) a single applicant institution that will be legally and financially responsible for the use and disposition of funds awarded; and (5) support provided, as necessary, for "Core" resources or facilities, each of which is expected to be utilized by at least two research projects in order to facilitate the research effort. Details of the responsibilities, relationships and governance of a study funded under a cooperative agreement are discussed later in this document under the section "Terms and Conditions of Award."

Applicants must propose a 5-year plan in order to maintain the integrity of the Cooperative Study Group.

FUNDS AVAILABLE

The estimated total funds, direct and facilities & administrative (F&A), available for the first year of support for this RFA will be $7 million. In fiscal year 2001, the sponsoring organizations plan to make 5 awards related to this RFA. Additional funds, approximately $2.5 million per year, will be made available to successful applicants. This level of support is dependent on the receipt of a sufficient number of applications of high scientific merit.

First-year budget requests may not exceed $900,000 total costs. Additional funds, approximately $2.5 million per year, will be available to successful applicants to support Innovative Projects,

Clinical Studies, and/or Cooperative Resources based on Steering Committee recommendations (see SPECIAL REQUIREMENTS, below).

The usual PHS policies governing grants administration and management will apply. Although this program is provided for in the financial plans of the NIH, awards pursuant to this RFA are contingent upon the availability of funds for this purpose. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and availability of funds.

At this time, the NIH has not determined whether or how this solicitation will be continued beyond the present RFA.

RESEARCH OBJECTIVES

Background

Autoimmune diseases, which disproportionately afflict women, are debilitating, chronic illnesses that affect multiple organ systems. Type 1 diabetes afflicts over 600,000 persons in the United States with peak onset in childhood. Although insulin treatment is available, long-term complications include kidney failure, blindness, amputations, and accelerated cardiovascular disease. Sjögren's syndrome, which affects predominantly middle-aged women, results in diminished lacrimal and salivary gland function. Patients may suffer dysphagia, atrophic gastritis, esophageal mucosal atrophy, constipation, and sub clinical pancreatic insufficiency. About 30% of patients with rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis suffer secondary Sjögren's syndrome, while 2 to 5 % of people aged 60 and above have primary Sjögren's syndrome. Multiple sclerosis afflicts over 350,000 persons in the United States; women are affected twice as frequently as men. Although the course of the disease is unpredictable, the central and peripheral nerve impairment can lead to blindness, weakness, loss of bowel and bladder control, and confinement to a wheelchair. Rheumatoid arthritis, which also affects primarily women, usually at an older age, causes chronic pain, crippling deformity, and loss of independence. This disease afflicts over 2% of the U.S. population. The 1999 Institute of Medicine report, "Vaccines for the 21st Century: A Tool for Decision Making," concluded that the development of vaccines to treat or prevent type 1 diabetes, multiple sclerosis, and rheumatoid arthritis would bring exceptionally high economic and health benefits. Preventive vaccines for other autoimmune diseases, including the less common but devastating pediatric autoimmune diseases such as juvenile rheumatoid arthritis and Kawasaki's disease would also enhance the public health. The Congressionally established Diabetes Research Working Group's 1999 report

entitled “Conquering Diabetes: A Strategic Plan for the 21st Century,” [http://mantis.cit.nih.gov/temp/diabetes/cd.pdf] highlighted basic and clinical research into the pathogenesis and prevention of type 1 diabetes as an extraordinary opportunity to significantly improve the future health of the nation.

Recent evidence suggests that autoimmunity or the autoimmune process may precede the development of clinical disease by years in type 1 diabetes and other autoimmune diseases. Although loss of beta cell function with development of hyperglycemia defines the diagnosis of type 1 diabetes, evidence of autoimmunity manifested by multiple autoantibodies to islet antigens may be apparent years earlier. In addition, evidence of autoimmunity in healthy individuals (e.g., multiple autoantibodies in family members of patients with type 1 diabetes who do not develop disease, e.g., non-progressors) suggests that mechanisms to control autoimmunity may be operative in immune homeostasis in healthy individuals. Similarly, synovial cell activation and inflammation in rheumatoid arthritis may precede the onset of multiarticular pain and cartilage destruction, the hallmarks of this disease. Increased understanding of the processes for containment of autoimmunity found in healthy individuals, novel strategies to control or prevent autoimmunity prior to the onset of clinical disease, and safe and rational application of these strategies to humans are needed.

Since the onset of the autoimmune process may precede by years the diagnosis, a further understanding of neonatal and pediatric immune homeostasis is needed, both in healthy and autoimmune prone individuals. Intervention at the earliest possible stage may be optimal for preventing these diseases.

Type 1 diabetes and other autoimmune diseases have been prevented in animal models using a variety of agents, hypothesized to be acting as toleragens or immunomodulators. However, our understanding of the mechanism and consequences of these approaches in animals is ncomplete. Likewise, information on immune homeostasis of autoimmune responses in humans is lacking. Nevertheless, the ability to selectively prevent development of or control the activity of autoreactive cells prior to onset of clinical disease without impairing protective immune responses appears feasible.

Research Objectives and Scope

This RFA will support a cooperative study group focused on research for the prevention of human autoimmune disease. For the purpose of this RFA, “prevention of autoimmune disease” is defined as halting the development of an autoimmune disease prior to clinical onset by

mechanisms other than global immunosuppression. The ultimate goal of this research is to develop the knowledge base necessary to design preventive interventions that could be administered efficiently and safely to at-risk individuals or to the general population, most likely infants or children. While the interventions may also be beneficial in established disease, the focus of this RFA is on prevention rather than therapy. Clinical studies are strongly encouraged wherever possible. Animal studies proposed under this RFA must document the relevance of the model to the development of preventive strategies for human autoimmune diseases. Each application must include at least one project focused directly on type 1 diabetes; applications that include projects on other autoimmune diseases or projects related to more than one autoimmune disease are particularly encouraged, however, applications may focus entirely on diabetes.

The Cooperative Study Group will be comprised of a consortium of investigators who, in collaboration with the NIH, will develop and implement a Study Group Plan for autoimmune disease prevention. The Study Group Plan will guide the allocation of additional resources to support Innovative Pilot Projects, Clinical Studies, and Cooperative Resources. The Study Group Plan will articulate the goals, specify the approaches, and define milestones for the activities of the Study Group [see “Study Group Plan” in SPECIAL REQUIREMENTS, below].

Research projects must contribute knowledge critical to achieving both of the following goals:

1. Advance the understanding of immune homeostasis in autoimmune diseased states as well as non-diseased states. This area includes studies of the immune control of autoantigen-specific T or B cells by mechanisms including peripheral deletion, anergy, or control by other protective cells, as well as research on the dysregulation of immune homeostatic mechanisms in autoimmune diseases. Research topics include, but are not limited to:

- Delineation of the phenotype and function of regulatory and effector T cell populations in target tissues and associated lymphoid organs;
- Development of the immune response to self in healthy and autoimmune prone infants and children;
- Definition of the role of the innate immune system in the maintenance and breakdown of immune homeostasis;
- Determination of the function of antigen processing and antigen presenting cell activity in the development and maintenance of self tolerance; and
- Definition of the role of genetic susceptibility and environmental influences on loss of homeostasis in autoimmune disease.

2. Design and develop interventions to prevent human autoimmune diseases, with special emphasis on type 1 diabetes. This includes the application of new information on the autoimmune disease process to facilitate the design of novel approaches and the improvement of promising strategies for autoimmune disease prevention. Research may include studies of the feasibility and mechanisms of preventive approaches in humans. Research topics include, but are not limited to:

o Practical approaches to target agents to desired cellular populations and to evaluate their effectiveness in vivo;
o Utilization of new adjuvants and delivery approaches to boost regulatory cells;
o Analyses of the consequences of intervention approaches on protective immunity and autoimmune responses;
o Practical means to identify populations most likely to benefit from specific interventions;
o Development and validation of bio-markers of disease risk, stage, activity, and immune responses; and
o Development and application of clinically relevant animal models to facilitate the translation of preventive approaches from animals to humans.

Studies of vaccines or therapeutics directed against infectious agents may be included if there is strong evidence for a causal relationship between the infectious agent and the occurrence of an autoimmune disease in the infected population.

Applicants are strongly encouraged to include clinical studies as an integral part of the required three projects. Such studies should be designed to investigate the mechanisms of autoimmune disease, develop or validate biomarkers of disease risk, and/or delineate the mechanisms of preventive strategies. Examples of clinical studies that may be proposed include: immunological studies of patient samples obtained from ongoing or completed clinical trials, and comparative analyses of immune responses in diseased and non-diseased individuals. This RFA will support only very limited phase 1 trials of the safety, toxicity or efficacy of candidate prevention approaches, which result from the research within this program. Clinical trials may not be submitted in the initial application and must be submitted and approved by the Steering Committee (see below) as clinical studies. If agents show promise, phase II and phase III clinical trials can be funded through collaborative arrangements with other programs, including the Autoimmunity Centers of Excellence, the Immune Tolerance Network, or the Diabetes Prevention Trial-Type 1/Diabetes TrialNet.

Specifically excluded are studies of globally immunosuppressive therapies.

SPECIAL REQUIREMENTS

A. Study Organization

1. Steering Committee

A Steering Committee will be established to serve as the main governing body of the Cooperative Study Group for Autoimmune Disease Prevention (hereinafter referred to as the Study Group). At a minimum, the Steering Committee will be composed of the principal investigators of each of the awarded grants, the Chairperson of the Adjunct Clinical Studies Subcommittee (see item 2 below), and an NIH representative. Each member of the Steering Committee will have one vote. The Steering Committee or the NIH may identify and appoint other members, as appropriate. A Chairperson will be selected by the Steering Committee from among the non-federal Committee members. Subcommittees of the Steering Committee may be established as necessary. The Steering Committee will meet three times during the first year, and semi-annually thereafter. Each Steering Committee member will be expected to participate in all meetings and other Steering Committee activities, e.g., conference calls, special subcommittees, etc., as may be necessary to accomplish the work of the Study Group.

The Steering Committee will be responsible for developing the Study Group Plan (see item 3 below), which will outline the goals, approaches, and milestones for the activities of the Study Group. In addition, the Steering Committee will be responsible for ensuring that the activities of all Study Group investigators are coordinated, collaborative when appropriate, directed toward the goal of developing prevention strategies for human autoimmune diseases, and productive. The Steering Committee will review the progress of all projects on an annual basis and make recommendations for: continuation or redirection of ongoing projects; incorporation of additional expertise needed for accomplishing goals; and future directions.

The Steering Committee will have access to additional NIH funds to support: 1) Innovative Pilot Projects; 2) Clinical Studies; and 3) Cooperative Resources in order to accomplish the goals of the Study Group. The Steering Committee's responsibility to conduct and oversee Innovative Pilot Projects, Clinical Studies, and Cooperative Resources is intended to encourage cooperative, collaborative, and directed efforts of the participating members.

2. Adjunct Clinical Studies Subcommittee

The Steering Committee shall appoint an Adjunct Clinical Studies Subcommittee to have primary responsibility for assisting the Study Group investigators in accessing, developing, designing, and implementing clinical studies to investigate the mechanisms of immune homeostasis in autoimmune diseased states as well as non-diseased states and the mechanisms of preventive strategies in humans. The Clinical Studies Subcommittee will be responsible for reviewing and making recommendations to the Steering Committee with regard to the implementation of clinical studies proposed by Study Group Members, and for coordinating these studies to facilitate collaboration and efficient use of clinical samples. Clinical studies approved in the initial application will not require Steering Committee approval but will undergo progress reviews. The members of the Clinical Studies Subcommittee shall include one NIH representative as well as representatives selected by the Principal Investigators, with each site appointing one member. Each member will have one vote. The Chair of the Adjunct Clinical Studies Subcommittee will be elected from among the non-federal members and shall serve as a voting member of the Steering Committee. The Subcommittee will meet in conjunction with Steering Committee meetings. Subcommittee members will be expected to participate in all Subcommittee meetings and other Subcommittee activities.

3. Study Group Plan

The Steering Committee shall develop the Study Group Plan, which will articulate the goals, specify the approaches, and define milestones for the activities of the Study Group in understanding immune homeostasis in diseased and non-diseased states, the consequences of manipulation of immune responses, and the development of strategies for the prevention of autoimmune diseases. The Plan shall include procedures and criteria for reviewing and for assessing progress on an annual basis and in developing recommendations for future directions. The Steering Committee will submit a draft Study Group Plan to the NIH within 3 months of award, and the final plan within 6 months of award.

4. Innovative Pilot Projects

Innovative Pilot Projects will be an integral part of this program. Proposals from Study Group members for innovative, exploratory, high-risk/high-yield, novel, and/or pilot research to advance the goals of the Study Group will be supported with resources available to the Steering Committee. The Steering Committee will develop procedures for the submission of proposed pilot projects, and criteria for the evaluation and selection of pilot projects to be implemented by the Study Group. The Steering Committee may approve more than one Innovative Pilot Project

at any single Study Group site. Innovative Pilot Projects may be funded for a period of 6 months up to a maximum of 2 years duration with budgets ranging from $50,000 to approximately $150,000 total costs per year as recommended by the Steering Committee.

5. Clinical Studies

It is anticipated that many opportunities for new clinical studies will arise within the Study Group as a result of new collaborations, expanded access to patients and clinical samples, and development of new hypotheses relevant for human autoimmune disease. To capitalize on these anticipated opportunities, additional clinical studies will be supported with resources available to the Steering Committee. Clinical studies must address the goals of the Study Group, including investigation of the mechanisms of autoimmune disease, development and/or validation of biomarkers of disease risk, and/or delineation of the mechanisms underlying preventive strategies. This program will support only very limited phase 1 trials of the safety, toxicity or efficacy of candidate prevention approaches, which result from the research within this program. Clinical trials may not be submitted in the initial application and must be submitted and approved by the Steering Committee as clinical studies. If agents show promise, phase II and phase III clinical trials can be funded through collaborative arrangements with other programs, including the Autoimmunity Centers of Excellence, the Immune Tolerance Network, or the Diabetes Prevention Trial-Type 1/Diabetes TrialNet. The Adjunct Clinical Studies Subcommittee will be responsible for reviewing and evaluating proposals for additional clinical studies and making recommendations to the Steering Committee for proposals to be implemented by the Study Group. The Subcommittee will establish procedures and criteria for the submission and evaluation of proposed clinical studies, and will assist in study development, design, implementation, coordination, and analysis. All clinical trials will be reviewed and monitored by the appropriate NIAID Data and Safety Monitoring Board.

6. Cooperative Resources

The Steering Committee will establish and support Cooperative Resources that provide central assistance and technical expertise for the projects undertaken by the Study Group investigators. These Cooperative Resources will provide reagents and services, as needed, to all members of the Study Group. The Steering Committee will determine procedures for the designation of Cooperative Resources, and will determine the scope of work and level of support based on Study Group requirements. Non-administrative cores proposed by individual members of the Study Group in the application may be expanded by the Steering Committee to become Cooperative Resources (with addition of funds available to Steering Committee). See “Additional

Requirements for Application" below for special application instructions for non-administrative cores. Cooperative Resources may be housed at Study Group member sites or supported through a subcontract to other facilities.

7. Coordination with other NIH-sponsored programs

The Cooperative Study Group will coordinate their efforts with other NIH-funded programs. Information obtained by the Cooperative Study Group will facilitate the design of clinical trials of preventive agents. Equally, ongoing or planned clinical trials offer a unique source of patient samples for human immune response studies by Study Group investigators. NIH-sponsored programs that support clinical trials in autoimmune diseases include, but are not limited to, the Immune Tolerance Network, the Autoimmunity Centers of Excellence, and the Diabetes Prevention Trial-Type 1/Diabetes TrialNet.

8. Budgets

First-year budget requests may not exceed $900,000 total costs. Additional funds in the amount of approximately $2.5 million per year will be available to successful applicants to support initiation or expansion of Innovative Pilot Projects, Clinical Studies, and/or Cooperative Resources based on Steering Committee recommendations.

9. Meetings

Applicants must include costs for participation of the Principal Investigator in all Steering Committee meetings and for an additional appointee for the Adjunct Clinical Studies Subcommittee. There will be three Steering Committee meetings in the first year, and semi-annual meetings each year thereafter. For budgetary purposes, applicants should assume meetings will be 1½ days in duration and held in Bethesda, MD. One of the semi-annual meetings will include presentation of scientific accomplishments for all projects by the Principal Investigators.

B. Minimum Requirements for Application

1. A broad range of scientific and technical expertise is required to carry out the objectives of this RFA, including extensive experience in: the study of basic animal and human immunology; mechanisms of autoimmunity and specific autoimmune diseases, including type 1 diabetes; genetics; molecular and cellular biology, particularly as applied to the identification and evaluation

of biomarkers and assay development and validation; and human research involving clinical samples. Applications must include scientific expertise in these areas under the direction of a senior scientist, serving as the Principal Investigator, with the responsibility for the scientific, technical, and administrative coordination and management of the applicant group. The Principal Investigator is advised to devote at least 20% effort to this program in the first year.

2. A minimum of three research projects must be proposed. At least one project must specifically address type 1 diabetes. Applications that include projects on other autoimmune diseases or projects related to more than one disease are particularly encouraged, however, applications may focus entirely on diabetes.

3. Support may be requested for core resources or facilities, each of which is expected to be utilized by at least two research projects in order to facilitate the research effort. The costs for these cores must be included within the budget request limit of $900,000 first year total costs. Cores may be funded as proposed to support at least two of the research projects, or they may be modified by the Steering Committee in order to most effectively serve the needs of the Study Group members. Such modifications may include consolidating core resources with centralized cooperative resources, or expanding core resources and facilities to serve as Cooperative Resources for multiple members of the Group. Cooperative Resources, which support the whole Study Group and are approved by the Steering Committee, will receive additional funds. Applicants who wish to serve as Cooperative Resources must: describe the capabilities of the investigators and the institutions to expand the proposed function/activity to fulfill the needs of the group; present an overall plan describing how an increase of up to five-fold would be implemented and managed; and develop and submit a separate budget detailing the projected additional personnel, supplies, and facility costs involved in such an expansion as well as the estimated cost per unit of service. The plan for expansion of the proposed cores to serve as Cooperative Resources will be reviewed for technical merit but will not affect the overall score of the application.

4. Innovative Pilot Projects: Application must include two proposed pilot projects to demonstrate applicant's capabilities to conceptualize and design novel studies. These proposed pilot projects will be peer reviewed and their technical merit reflected in determining the overall score of the application. Award of the Cooperative Agreement does not imply that any of the proposed pilot projects will be implemented. The pilot projects to be conducted by the Study Group will be selected by the Steering Committee and, therefore, the actual pilot projects may not reflect any single proposed project submitted in response to this RFA. Both proposed pilot projects should be described in 2-5 pages in the application immediately following the Overview section.

Proposed costs for these projects must be included, but detailed categorical budgets should not be included. Costs for innovative pilot projects should not be included in the calculation of total first year program costs.

5. The application must include a written commitment to accept the participation and assistance of NIH staff in accordance with the guidelines outlined under "Terms and Conditions of Award: NIH Staff Responsibilities." The application must also include a written commitment to the cooperative organization, including agreement to intellectual property rights certification as indicated under “Terms and Conditions of Award,” (see below) and willingness to serve and commit appropriate effort to the work of the Steering Committee. In addition, the applicants must agree to adhere to the decisions reached by that Steering Committee, including selection of core facilities, Cooperative Resources, Innovative Pilot Projects, Clinical Studies, and annual review of all projects funded under this program.

TERMS AND CONDITIONS OF AWARD

The following terms and conditions will be incorporated into the award statement and provided to the Principal Investigator as well as the institutional official at the time of award.

Cooperative agreements are subject to the administrative requirements outlined in OMB circulars A-102 and A-110. All pertinent HHS, PHS, and NIH grant regulations, policies and procedures, with particular emphasis on PHS regulations at 42 CFR Part 52 and HHS regulations at 45 CFR Parts 74 and 92, are applicable.

The administrative and funding instrument used for this program is the multiproject cooperative agreement (U19), an "assistance" mechanism rather than an "acquisition" mechanism, in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during the performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardees for the project as a whole, although specific tasks and activities in carrying out the research will be shared among the awardees and the NIH Scientific Coordinators.

1. MONITORING CLINICAL STUDIES. When clinical studies are a component of the research proposed, NIAID policy requires that studies be monitored commensurate with the degree of

potential risk to study subjects and the complexity of the study. Terms and Conditions of Award will be included with awards. NIAID policy was announced in the NIH Guide on February 24, 2000 and is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-AI-00-003.html. The full policy including terms and conditions of award is available at: http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf

2. Awardee Rights and Responsibilities

Awardees will have primary responsibility for defining the research objectives, approaches and details of the projects within the guidelines of the RFA and for performing the scientific activity. Specifically, awardees have primary responsibility as described below.

Steering Committee

A Steering Committee will be established to serve as the main governing body of the Cooperative Study Group for Autoimmune Disease Prevention (hereinafter referred to as the Study Group). At a minimum, the Steering Committee will be composed of the principal investigators of each of the awarded grants, the Chairperson of the Adjunct Clinical Studies Subcommittee (see below), and an NIH representative. Each member of the Steering Committee will have one vote. The Steering Committee or the NIH may identify and appoint other members, as appropriate. A Chairperson will be selected by the Steering Committee from among the non-federal Committee members. Subcommittees of the Steering Committee may be established as necessary. The Steering Committee will meet three times during the first year, and semi-annually thereafter. Each Steering Committee member will be expected to participate in all meetings and other Steering Committee activities, e.g., conference calls, special subcommittees, etc., as may be necessary to accomplish the work of the Study Group.

The Steering Committee will be responsible for developing the Study Group Plan (see below), which will outline the goals, approaches, and milestones for the activities of the Study Group. In addition, the Steering Committee will be responsible for ensuring that the activities of all Study Group investigators are coordinated, collaborative when appropriate, directed toward the goal of developing prevention strategies for human autoimmune diseases, and productive. The Steering Committee will review the progress of all projects on an annual basis and make recommendations for: continuation or redirection of ongoing projects; incorporation of additional expertise needed for accomplishing goals; and future directions.

The Steering Committee will have access to additional NIH funds to support: 1) Innovative Pilot Projects; 2) Clinical Studies; and 3) Cooperative Resources in order to accomplish the goals of the Study Group. The Steering Committee's responsibility to conduct and oversee Innovative Pilot Projects, Clinical Studies, and Cooperative Resources is intended to encourage cooperative, collaborative, and directed efforts of the participating members.

Adjunct Clinical Studies Subcommittee

The Steering Committee shall appoint an Adjunct Clinical Studies Subcommittee to have primary responsibility for assisting the Study Group investigators in accessing, developing, designing, and implementing clinical studies to investigate the mechanisms of immune homeostasis in autoimmune diseased states as well as non-diseased states and the mechanisms of preventive strategies in humans. The Clinical Studies Subcommittee will be responsible for reviewing and making recommendations to the Steering Committee with regard to the implementation of clinical studies proposed by Study Group Members, and for coordinating these studies to facilitate collaboration and efficient use of clinical samples. Clinical studies approved in the initial application will not require Steering Committee approval but will undergo progress reviews. The members of the Clinical Studies Subcommittee shall include one NIH representative as well as representatives selected by the Principal Investigators, with each site appointing one member. Each member will have one vote. The Chair of the Adjunct Clinical Studies Subcommittee will be elected from among the non-federal members and shall serve as a voting member of the Steering Committee. The Subcommittee will meet in conjunction with Steering Committee meetings. Subcommittee members will be expected to participate in all Subcommittee meetings and in other Subcommittee activities.

Study Group Plan

The Steering Committee shall develop the Study Group Plan, which will articulate the goals, specify the approaches, and define milestones for the activities of the Study Group in understanding immune homeostasis in diseased and non-diseased states, the consequences of manipulation of immune responses, and the development of strategies for the prevention of autoimmune diseases. The Plan shall include procedures and criteria for reviewing and for assessing progress on an annual basis and in developing recommendations for future directions. The Steering Committee will submit a draft Study Group Plan to the NIH within 3 months of award, and the final plan within 6 months of award.

Innovative Pilot Projects

Innovative Pilot Projects will be an integral part of this program. Proposals from Study Group members for innovative, exploratory, high-risk/high-yield, novel, and/or pilot research to advance the goals of the Study Group will be supported with resources available to the Steering Committee. The Steering Committee will develop procedures for the submission of proposed pilot projects, and criteria for the evaluation and selection of pilot projects to be implemented by the Study Group. The Steering Committee may approve more than one Innovative Pilot Project at any single Study Group site. Innovative Pilot Projects may be funded for a period of 6 months up to a maximum of 2 years duration with budgets ranging from $50,000 to approximately $150,000 total costs per year as recommended by the Steering Committee.

Clinical Studies

It is anticipated that many opportunities for new clinical studies will arise within the Study Group as a result of new collaborations, expanded access to patients and clinical samples, and development of new hypotheses relevant for human autoimmune disease. To capitalize on these anticipated opportunities, additional clinical studies will be supported with resources available to the Steering Committee. Clinical studies must address the goals of the Study Group, including investigation of the mechanisms of autoimmune disease, development and/or validation of biomarkers of disease risk, and/or delineation of the mechanisms underlying preventive strategies. This program will support only very limited phase 1 trials of the safety, toxicity or efficacy of candidate prevention approaches, which result from the research within this program. Clinical trials may not be submitted in the initial application and must be submitted and approved by the Steering Committee as clinical studies. If agents show promise, phase II and phase III clinical trials can be funded through collaborative arrangements with other programs, including the Autoimmunity Centers of Excellence, the Immune Tolerance Network, or the Diabetes Prevention Trial-Type 1/Diabetes TrialNet. The Adjunct Clinical Studies Subcommittee will be responsible for reviewing and evaluating proposals for additional clinical studies and making recommendations to the Steering Committee for proposals to be implemented by the Study Group. The Subcommittee will establish procedures and criteria for the submission and evaluation of proposed clinical studies, and will assist in study development, design, implementation, coordination, and analysis. All clinical trials will be reviewed and monitored by the appropriate NIAID Data and Safety Monitoring Board.

Cooperative Resources

The Steering Committee will establish and support Cooperative Resources that provide central assistance and technical expertise for the projects undertaken by the Study Group investigators. These Cooperative Resources will provide reagents and services, as needed, to all members of the Study Group. The Steering Committee will determine procedures for the designation of Cooperative Resources, and will determine the scope of work and level of support based on Study Group requirements. Non-administrative cores proposed by individual members of the Study Group in the application may be expanded by the Steering Committee to become Cooperative Resources. Cooperative Resources may be housed at Study Group member sites or supported through a subcontract to other facilities.

Coordination with other NIH-sponsored programs

The Cooperative Study Group will coordinate their efforts with other NIH-funded programs. Information obtained by the Cooperative Study Group will facilitate the design of clinical trials of preventive agents. Equally, ongoing or planned clinical trials offer a unique source of patient samples for human immune response studies by Study Group investigators. NIH-sponsored programs that support clinical trials in autoimmune diseases include, but are not limited to, the Immune Tolerance Network, the Autoimmunity Centers of Excellence, and the Diabetes Prevention Trial-Type 1/Diabetes TrialNet.

Intellectual Property

Institutions' rights in inventions made under this funding mechanism and the reporting requirements for such inventions will be governed by Public Law 96-517 (the Bayh-Dole Act of 1980), 35 U.S.C. Secs. 200-212, 37 C.F.R. Part 401, and 45 C.F.R. Parts 6 and 8. Institutions and investigators are expected to share background technology and intellectual property on a non-exclusive and royalty-free basis with other participating institutions as required to carry out the aims of the collaborative projects. In the event of a joint invention involving multiple institutions, the co-inventors' institutions are expected to cooperate in the filing of any resulting patent applications and in developing a plan to achieve commercial application of the technology. Applicants are expected to abide by the "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources", as published in the Federal Register December 23, 1999, Volume 64, Number 246, Pages 72090-72096. The Study Group Steering Committee will be asked to develop a policy on publication and sharing of data obtained by the collaborative efforts of the Study Group.

3. NIH Staff Responsibilities

NIH staff assistance will be provided by Chief of the Autoimmunity Section, Clinical Immunology Branch, Division of Allergy, Immunology and Transplantation, NIAID and the Chief of the Molecular and Structural Immunology Section, Basic Immunology Branch, Division of Allergy, Immunology and Transplantation, NIAID, who will serve as NIH Scientific Coordinators. The NIH Scientific Coordinators will have substantial scientific/programmatic involvement along with representatives of the other sponsoring organizations during the conduct of this activity through technical assistance, advice and coordination above and beyond normal program stewardship for grants, as described below.

The NIH Scientific Coordinators along with representatives of the other sponsoring organizations will attend all Steering Committee meetings and participate in other Committee activities, including, but not limited to, development of the Study Group Plan, review and approval of Innovative Pilot Projects, Clinical Studies, and Cooperative Resources to be supported. The NIH Scientific Coordinators and representatives of the sponsoring organizations will share one vote.

The NIH Scientific Coordinators and representatives of the sponsoring organizations will participate in the Adjunct Clinical Studies Subcommittee activities, including the evaluation, approval, and guidance of clinical studies that require the consent of the Steering Committee. They will share one vote.

The NIH Scientific Coordinators will provide expertise in: technology and resource development, availability, and application; development, design, and implementation of clinical studies; policies and procedures for the protection of human subjects; and serve as a liaison to the Immune Tolerance Network, Autoimmunity Centers of Excellence, and the Diabetes Prevention Trial-Type 1/Diabetes TrialNet to facilitate collaboration and coordination between the development of prevention strategies within the Study Group and the testing of interventions within these other NIH-sponsored programs.

Organizational Changes

Certain organizational changes require the prior written approval of the NIAID Scientific Coordinators. These changes include the addition/substitution/removal of a principal investigator. A change in the designated principal investigator, or in any key personnel identified in the application, must have the prior written approval of the NIAID Grants Management Specialist in consultation with the NIAID Scientific Coordinators.

Program Review

The NIH Scientific Coordinators and representative of the sponsoring organizations will review the progress of the Cooperative Study Group through consideration of annual progress reports, periodic reports on ongoing progress, findings, and future plans presented during meetings and conference calls, publications, site visits, etc.

4. Collaborative Responsibilities

Collaborative responsibilities are as detailed above in this section on Terms and Conditions of Award under “Awardee Rights and Responsibilities” for the:

- Steering Committee;
- Study Group Plan;
- Innovative Pilot Projects;
- Clinical studies;
- Cooperative Resources; and,
- Intellectual Property

5. Arbitration

Any disagreement that may arise on scientific or programmatic matters (within the scope of the award) between award recipients and the NIAID may be brought to arbitration. An arbitration panel will be composed of three members -- one selected by the Steering Committee or by the individual awardee in the event of an individual disagreement, a second member selected by the NIAID, and the third member with expertise in the relevant area and selected by the two prior members will be formed to review any scientific or programmatic issue that is significantly restricting progress. While the decisions of the Arbitration Panel are binding, these special arbitration procedures will in no way affect the awardee's right to appeal an adverse action in accordance with PHS regulations at 42 CFR Part 50, subpart D, and HHS regulations at 45 CFR Part 16.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear, compelling rationale, and justification are provided that inclusion

is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the updated "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," August 2000 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html. The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual and conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and which is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html.

Investigators may obtain copies from these sources or from Dr. Elaine Collier or Dr. Charles Hackett (listed in INQUIRIES below) who may also provide additional relevant information concerning the policy.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

LETTER OF INTENT

Prospective applicants are asked to submit, by December 15, 2000, a letter of intent that includes a descriptive title of the overall proposed research, the name, address and telephone number of the Principal Investigator, and the number and title of this RFA. Although the letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of subsequent applications, the information that it contains allows NIAID staff to estimate the potential review workload and to plan the review.

The letter of intent is to be sent to Dr. Madelon Halula (see address under INQUIRIES) by the letter of intent receipt date listed.

APPLICATION PROCEDURES

Applicants for U19 cooperative agreements must follow special application guidelines in the NIAID Brochure entitled INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS; this brochure is available via the web at: http://www.niaid.nih.gov/ncn/tools/multibron.htm.

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants. Application kits are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301) 435-0714, email: GrantsInfo@nih.gov. Applications are also available on the World Wide Web at http://grants.nih.gov/grants/forms.htm.

Applications must be received by February 26, 2001.

Applications that are not received as a single package on the receipt date or that do not conform to the instructions contained in PHS 398 (rev. 4/98) Application Kit as modified in, and superseded by, the NIAID BROCHURE ENTITLED "INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS", and by SPECIAL INSTRUCTIONS FOR COMPLETION OF APPLICATIONS IN RESPONSE TO THIS RFA will be judged non-responsive and will be returned to the applicant.

For purposes of identification and processing, item 2a on the face page of the application must be marked “YES” and the RFA number “AI-00-016” and the words “COOPERATIVE STUDY GROUP FOR AUTOIMMUNE DISEASE PREVENTION” must be typed in.

The RFA label and line 2 of the application should both indicate the RFA number. The RFA label must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review.

The sample RFA label available at: http://grants.nih.gov/grants/funding/phs398/label-bk.pdf.has been modified to allow for this change. Please note this is in pdf format.

Submit a signed, typewritten original of the application, including the checklist, and three signed, exact, single-sided photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express mail or courier service)

At the time of submission, two additional exact copies of the grant application and all five sets of any appendix material must be sent to Dr. Madelon Halula listed in “Inquiries,” below.

Concurrent submission of an R01 and a Component Project of a Multi-project Application:
Current NIH policy permits a component research project of a multi-project grant application to be concurrently submitted as a traditional individual research project (R01) application. If, following review, both the multi-project application and the R01 application are found to be in the fundable range, the investigator must relinquish the R01 and will not have the option to withdraw from the multi-project grant. This is an NIH policy intended to preserve the scientific integrity of a multi-project grant, which may be seriously compromised if a strong component project(s) is removed from the program.

Investigators wishing to participate in a multi-project grant must be aware of this policy before making a commitment to the Principal Investigator and awarding institution.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for

conducting the proposed research. If so, a letter of agreement from either the GCRC program director or principal investigator could be included with the application.

SPECIAL INSTRUCTIONS FOR COMPLETION OF APPLICATIONS IN RESPONSE TO THIS RFA

Page limitations for all applications will be 25 pages for the scientific plan of each project; 2-5 pages for innovative projects; 10 pages for cores.

Applications may be submitted by single institutions or consortia of institutions as may be appropriate to provide the requisite types of expertise. All applications must include the information and materials specified under item "B. Minimum Requirements for Application."

Applicants for U19 cooperative agreements must follow special application guidelines in the NIAID Brochure entitled INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS; this brochure is available at: http://www.niaid.nih.gov/ncn/tools/multibron.htm.

This brochure presents specific instructions for sections of the PHS 398 (rev. 4/98) application form that should be completed differently than usual.

REVIEW CONSIDERATIONS

Review Procedures

Upon receipt, applications will be reviewed for completeness by the NIH Center for Scientific Review and for responsiveness by NIAID staff. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIH in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the National Advisory Councils of the sponsoring NIH Institutes.

Review Criteria

The general criteria for U19 multiproject cooperative agreement applications are presented in the NIAID brochure, INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS, available at: http://www.niaid.nih.gov/ncn/tools/multibron.htm

Additional review criteria specific to this RFA are:

Applicants must comply with the SPECIAL REQUIREMENTS and Minimum Requirements for Application (See above).

Schedule

Letter of Intent Receipt Date: December 15, 2000
Application Receipt Date: February 26, 2001
Scientific Review Date: June 2001
Advisory Council Date: October, 2001
Earliest Date of Award: August 15, 2001

AWARD CRITERIA

Funding decisions will be made on the basis of scientific and technical merit as determined by peer review, program balance, and the availability of funds.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Requests for the NIAID brochure "INSTRUCTIONS FOR APPLICATIONS FOR MULTI-PROJECT AWARDS" as well as inquiries regarding programmatic (research scope and eligibility) issues, may be directed to:

Elaine Collier, M.D.
Chief, Autoimmunity Section
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Room 5135, MSC-7640
6700-B Rockledge Drive

Bethesda, MD 20892-7640
Telephone: (301) 496-7104
FAX: (301) 402-2571
E-Mail: ec5x@nih.gov

Charles J. Hackett, Ph.D.
Chief, Molecular and Structural Immunology Section
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Room 5139, MSC-7640
6700-B Rockledge Drive
Bethesda, MD 20892-7640
Telephone: (301) 496-7551
FAX: (301) 402-2571
E-Mail: ch187q@nih.gov

Joan Harmon, Ph.D.
Senior Advisor for Diabetes
Division of Diabetes, Endocrinology and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Blvd., Room 697
Bethesda, MD 20892-
TEL: 301 594-8813
FAX: 301 480-3503
Email: joan_harmon@nih.gov

Dr. Gilman Grave
Chief, Endocrinology Nutrition & Growth Branch
National Institute of Child Health and Human Development
6100 Executive Blvd., Room 4B11A, MSC 7510
Bethesda, MD 20892-7510
Phone: (301) 496-5593
FAX: (301) 480-9791
Email: graveg@exchange.nih.gov

Susana Serrate-Sztein, M.D.
Rheumatic Diseases Branch

National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A25
Bethesda MD 20892-6500
Telephone: (301) 594-5032
FAX (301) 480-4543
Email: szteins@mail.nih.gov

Kenneth A. Gruber, Ph.D.
Chief, Chronic & Disabling Diseases Branch
Division of Extramural Research
National Institute of Dental and Craniofacial Research
Room 4AN-18C, Bldg 45
Bethesda, MD 20892
Tel: 301-594-4836
FAX: 301-480-8318
Email: kenneth_gruber@nih.gov

Direct inquiries regarding preparation of the application and review issues, address the letter of intent to, and mail two copies of the application and all five sets of appendices to:

Dr. Madelon Halula
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Room 2150, MSC-7616
6700-B Rockledge Drive
Bethesda, MD 20892-7616
Telephone: (301) 402-2636
FAX: (301) 402-2638)
Email: mhalula@niaid.nih.gov

Direct inquiries regarding fiscal matters to the following Institute contacts:

Pamela Fleming
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Room 2119, MSC-7614
6700-B Rockledge Drive

Bethesda, MD 20892-7614
Telephone: (301) 402-6580
FAX: (301) 480-3780
E-mail: pfleming@niaid.nih.gov

Florence Danshes
Division of Extramural Affairs
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Boulevard, Room 634
Bethesda, MD 20892-5456
Telephone: (301) 594-8861
FAX: (301) 480-3504
Email: danshesf@extra.niddk.nih.gov

E. Douglas Shawver
Grants Management Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 8A17
Bethesda, MD 20892-7510
Telephone: (301) 496-1303
FAX: (301) 402-0915
Email: shawverd@hd01.nih.gov

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A49
Bethesda MD 20892-6500
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: mn23z@nih.gov

Martin R. Rubinstein
Division of Extramural Research
National Institute of Dental and Craniofacial Research
Building 45, Room 4AN-44A
Bethesda, MD 20892-6402

Telephone: (301) 594-4800
Fax: (301) 480-8301
Email: Martin.Rubinstein@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalogue of Federal Domestic Assistance No. 93.855 - Immunology, Allergy, and Transplantation Research, No. 93.865 – Research for Mothers and Children, No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research, No. 93-847 – Diabetes, Endocrinology, and Metabolic Diseases, and No. 93.121 – Oral Diseases and Disorders Research. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH Grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The Public Health Service strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or, in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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